REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing remarks.

The pending claims

Claims 1-21 and 34-37 are pending in this application, with claims 1-20 being withdrawn from consideration and claims 22 -33 being canceled. Claims 21 and 34-37 are currently under examination.

The 35 USC § 103(a) rejection

Claims 21 and 34-37 stand rejected under 35 USC § 103(a) over Meyers et al. (US 2002/0009779) in view of Liang et al. (J. of Biological Chemistry, 1990 Vol. 265:16863-16866). The rejection is respectfully traversed.

The Supreme Court in KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007) recently affirmed the factual analysis set forth in Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18 (1966) Id. at 1734. Known as the "Graham factors", the appropriate obviousness analysis requires an inquiry into: 1) the scope and content of the prior art; 2) the differences between the prior art and the claims at issue; and 3) the level of ordinary skill in the art.[1] The court further affirmed that considerations of any teachings, suggestions, or motivations for combining previous known elements and whether or not such combinations would have led to predictable results can form an important part of the analysis. In particular, the Court in KSR states that:

> "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results..."

[1] For the sake of argument, the level of skill in the art is assumed to be a person having a baccalaureate degree in the biological or pharmaceutical sciences.

It is not predictable that the combination of Liang et al. and Meyers et al. will lead to a viable method for identifying an agent for treating diabetes.

Claims 21 and 34-37 are directed to use of a multi-step assay for selecting an agent that would improve the insulin response of a diabetic or pre-diabetic animal to glucose. To provide the necessary motivation to use a screening protocol, it must be established with high certainty that the recited polypeptide is actually involved in the insulin secretion pathway. Validation of the participation of the polypeptide in the pathway is necessary to ensure that the assay is an appropriate procedure for use in predictably screening agents to identify one for improving insulin secretion.

Thus, prior to its use there must exist a *high expectation* that the assay *will be a viable one* for identifying an agent. Knowing that inhibiting the recited polypeptide can influence glucose induced insulin secretion is also necessary in understanding and interpreting the test results. For example, if in using the assay it was found that an inhibitor does not increase insulin secretion in response to glucose, the meaning of this result would be unclear if there are doubts as to whether the polypeptide is even involved in the disease pathway. That is, the lack of a positive test result would raise the possibility that the recited polypeptide does not play a role in the glucose induced insulin secretion pathway if this option cannot be ruled out at the onset.

Upon evaluation of the Graham factors, applicants will show that the combination of Meyers et al. and Liang et al. together do not provide the assurance and expectation that agents that inhibit the claimed polypeptide will also improve glucose induced insulin response.

The Scope and Content of the Prior Art

The Scope and Content of Meyers et al. (US 2002/0009779)

Meyers et al. teaches (paragraphs **[0001]** to **[0003]**) that there are four separate types of hexokinases, with hexokinase IV being known as glucokinase and that they have identified a new hexokinase that they refer to as 50365 (in the present application, this polypeptide corresponds to SEQ ID No. 2 and is also referred to as hexokinase V).

Applicants do not dispute the assertion of Meyers et. al. that agents binding to 50365 can be used to treat 50365 mediated disorders. While Meyers et. al. speculates that 50365 inhibition may be used to treat diabetes, there is no teaching to support this speculation. More specifically, Meyers et al. does not provide any showing that 50365 is involved in pathways mediating glucose induced insulin secretion. Insulin is secreted in the islet β cells of the pancreas, but Meyers et. al. does not disclose that 50365 is found in the pancreas and instead show that 50365 mRNA is up-regulated in other cell types, particularly cancer cells. Applicants submit that Meyers et al. does show any predictability that screening agents that bind to 50365 will lead to the identification of an agent that will also enhance insulin response to glucose, as Meyers et al. is wholly silent on whether 50365 is even present in the pancreatic cells of diabetic or prediabetic animals. Without any teaching that 50365 can be found in pancreatic cells, there can also be no teaching that aberrant 50365 expression in such cells is related to diabetes.

The Scope and Content of Liang et al. (J. of Biological Chemistry, 1990 Vol. 265:16863-16866)

Liang et al. discloses experiments to study the relationship of hexokinases to glucose induced insulin response in rat pancreatic islet cells. At the time of the disclosure of Liang et al., the hexokinase 50365 had not yet been specifically identified. The experiments of Liang et al. however, led to a singular result that of all the hexokinases, it is *only* glucokinase (hexokinase IV) that mediates glucose induced insulin secretion.

Applicants had previously pointed out that 50365 / hexokinase V share greater sequence homology with hexokinases I and II than with hexokinase IV. Coupled with the findings of Liang et al., these teachings do not provide any support to the notion that 50365/hexokinase V is involved in the glucose induced insulin secretion pathways of prediabetic or diabetic animals. As such, Liang et al. does not teach that assays directed to testing hexokinase inhibitors other than those of hexokinase IV would be of value in identifying agents for treating diabetes.

The Differences Between the Cited Art and Claims

Unlike the teachings of the cited references, the present application teaches however that the insulin producing islet cells of diabetic mice over-express hexokinase V and that there is a

previously unknown and an unexpected link between hexokinase V expression and glucose induced insulin secretion. In particular, Figure 10 of the present application shows the release of insulin as a function of glucose concentration. In the control cells over-expressing a control protein (GFP, green fluorescent protein was chosen because it is not coupled to the insulin secretion pathway), insulin release increases as expected with increasing glucose concentrations of 2mM, 5mM, and 16mM. Surprisingly, cells over expressing hexokinase V show comparably lower insulin release at the higher 16mM glucose concentration. This unexpected finding suggests that over-expressing hexokinase V disrupts insulin secretion in response to glucose. This finding is in stark contrast to those of Liang et. al. that only hexokinase IV mediates glucose induced insulin secretion (see Table 1 of Liang et. al.). These experiments and results are neither suggested nor expected based on the teachings of Meyers et al. or Liang et al., either alone or in combination. Thus only the teachings of the present application would motivate one of skill in the art to identify agents according to the steps of the pending claims and in particular according to the step of determining the insulin secretion response to glucose of animals treated with an inhibitor of hexokinase V.

Thus, it is not predictable that the combination of Liang and Meyers will lead to a viable method for identifying an agent for treating diabetes, as neither provide any evidence to support an expectation that agents that bind hexokinase V will also improve glucose induced insulin secretion in prediabetic or diabetic animals.

For the reasons stated, withdrawal of the rejection under 35 USC § 103(a) of Claims 21 and 34-37 is respectfully requested.

Applicants respectfully submit that all pending rejections have been addressed and that the present application is now in condition for allowance. Favorable reconsideration and allowance of the pending claims is respectfully requested. Notwithstanding the above, Applicants enclose with this response a notice of appeal to avoid unintentional abandonment of the application. If the Examiner believes a telephone conversation would help advance

prosecution of the present application, the Examiner is cordially invited to contact the undersigned at the number below.

Respectfully submitted,

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